

TABLE 4-continued

Summary of Antiviral Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine					
Virus	Cell	EC ₅₀ , CPE (μM)	EC ₅₀ , NR ^a (μM)	CC ₅₀ , CPE (μM)	CC ₅₀ , NR ^a (μM)
Yellow Fever	Vero	19/3.2	32/12	>100	>100
Influenza A (H1N1)	MDCK	>100	>100	>100	>100
Influenza A (H3N2)	MDCK	>100	>100	>100	>100
Influenza B	MDCK	>100	>100	>100	>100
Rhinovirus	KB	25	20	>100	>100
Type 2 VEE	Vero	>100	>100	>100	>100
SARS-CoV	Vero	>100	>100	>100	>100

^aNR = Neutral Red.

TABLE 5

Summary of Antiviral Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine			
Virus	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (EC ₉₀ , μM)	2'-C-methylcytidine (EC ₉₀ , μM)	2'-C-methyladenosine (EC ₉₀ , μM)
BVDVncp	>22	0.5	1.2
BVDVcp	>100	2	1.5
RSV	>100	>100	>100
HIV ^a	>100	ND	ND
HBV	>10	>10	ND
Coronavirus 229E	>100	ND	ND

ND = Not determined.

TABLE 6

Cytotoxicity Studies ^a			
Cell Line	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine CC ₅₀ , μM	2'-C-methylcytidine CC ₅₀ , μM	2'-C-methyladenosine CC ₅₀ , μM
CloneA	>100	>100	37
Huh7	>100	>100	30
HepG2	75	>100	58
MDBK	>100	>100	
PBM	>100		
CEM	>100		
Vero	>100		
MRC-5	>100		

^aResults determined using MTS assay.

TABLE 7

Mitochondrial Toxicity Study		
Compound	mtDNA Synthesis (IC ₅₀ , μM)	Lactic Acid Increase
(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine	>25	No effect ≥33 μM
2'-C-methylcytidine	>25	No effect ≥33 μM

TABLE 8

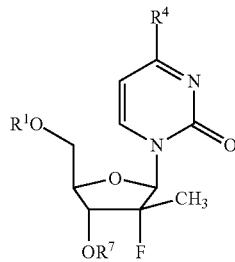
Preliminary PK Parameters in Rhesus Monkeys Following a Single Oral Dose of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine at 33.3 mg/kg			
Parameter	Units	Mean ± SD	
C _{max}	μM	9.6 ± 2.7	
T _{max}	hours	2 ± 1	
AUC _{0-last}	μM × h	44.2 ± 22.2	
T _{1/2}	hours	3.9 ± 0.1	
Bioavailability	F. %	21 ± 11	

Effect of Nucleoside Analogs on Human Bone Marrow Cells			
Compound (β-D-analog)	BFU-E IC ₅₀ (μM)	CFU-GM IC ₅₀ (μM)	
2'-fluoro-2'-C-methylcytidine	98.2	93.9	
2'-C-methylcytidine	20.1	13.2	
AZT	0.08	0.95	

TABLE 9

The invention claimed is:

1. A method of inhibiting the proliferation of hepatitis C virus in a human subject infected with the virus comprising providing to the subject an antivirally effective amount of a compound of the structure:

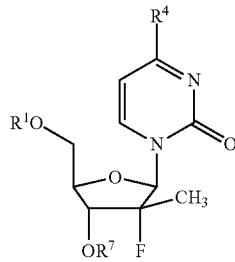


or its pharmaceutically acceptable salt wherein R¹ and R⁷ are both H;

and

R⁴ is NH₂.

2. A method of inhibiting the proliferation of a hepatitis C virus in a human subject infected with the virus comprising providing to the subject an antivirally effective amount of a compound of the structure:



or its pharmaceutically acceptable salt

wherein R¹ is monophosphate; R⁷ is H; and R⁴ is NH₂.